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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/383,695	08/26/99	NEVILLE	D 14014.0225

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1642	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/383,695	Applicant(s) Neville et al
	Examiner Ungar	Group Art Unit 1642

☒ Responsive to communication(s) filed on *Jan 19, 2001*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-10 and 22* is/are pending in the application.

Of the above, claim(s) *5, 7, and 8* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-4, 6, 9, 10, and 22* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5,6*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ Notice to Comply

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. The Election filed January 9, 2001 (Paper No. 12) in response to the Office Action of December 5, 2000 (Paper No. 9) is acknowledged and has been entered. Claims 5, 7 and 8 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 1-4, 6, 9-10 and 22 are pending in the application and are currently under prosecution.

2. Applicant's election with traverse of the species of allogeneic and deoxyspergualin, claims 4 and 9 in Paper No 12 is acknowledged. The traversal is on the ground(s) that if the genus claim is patentable, applicant is entitled to a reasonable number of specific species. The argument has been considered but has not been found persuasive because, for the reasons set forth below, the generic claim is not patentable. Applicant further argues that Applicant is not required to elect a species when applicants have not claimed an unreasonable number of species. The argument has been considered but has not been found persuasive because CFR § 1.146 specifically states that in the first action on an application containing a generic claim and claims restricted separately to each of more than one species embraced thereby, the examiner may require the applicant in his response to that action to elect that species of his or her invention to which his or her claim shall be restricted if no generic claim is held allowable. For these reasons the election of species is deemed to be proper and is therefore made FINAL.

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CAR 1.8821 (a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CAR 1.821 through 1.825 for the reasons(s) set forth on the attached Notice to

Comply with Requirements for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Further, it is noted that this application is a division of patent application 08/843,409 which has a CRF which is technically correct and entered in our database and is available for use. This information may be imported into the current application by the filing of an appropriate request to use a CRF from another application.

The following paragraph, or language having the same effect, can be used to invoke the procedures of 37 CAR section 1.821(e) in which an identical computer readable form from another application is used in a given application. The paragraph should be incorporated into a separate paper to be submitted in the given application.

> The computer readable form in this application, XXXXXXXX is identical with that filed in Application number XXXXXXX filed XXXXXXXXXX. In accordance with 37 CAR 1.821(e), please use the [first-filed, last filed or only, whichever is applicable] computer readable form filed in that application as the computer readable form for the instant application. It is understood that the Patent and Trademark Office will make the necessary change in application number and filing date for the computer readable form that will be used for the instant application. A paper copy of the sequence listing is [included in the originally-filed specification of the instant application, included in a separately filed preliminary amendment for incorporation into the specification, whichever is applicable].

Further, it is noted that the sequences listed on page 67, Table 6 are not accompanied by unique identifying SEQ ID NOS. Since these sequences contain greater than ten nucleotides they are required to conform to the sequence rules. These sequences must have SEQ ID Nos assigned to them which correspond to the

same numbers in a computer readable form and a paper copy of the sequence listing. Please see the attached Notice To Comply. Further, Examiner has made an effort to identify these informalities but applicant must carefully review the specification to identify and indicate where unidentified sequences that do not comply with the sequence rules may be found. Appropriate correction is required.

4. It is noted that a priority date of April 15, 1996 has been established for the currently claimed invention because a review of the earlier provisional application 60/015,459 did not reveal disclosure of sFv-DT390 and application numbers 08/739,703 and 60/008,104 are unavailable to Examiner at this time. If applicant disagrees with any rejection set forth in this office action based on examiner's establishment of a priority date of April 15, 1996 for the instantly claimed application serial number 09/383,695, Applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

5. It is noted that the references disclosed in the information disclosure form drawn to references found in application number 08/739,703 have not been considered. The references have not been considered because they are not available to Examiner at this time. Applicant might consider resubmitting the references for consideration.

Specification

6. The specification on page 1 should be amended to reflect the status of the parent application serial numbers 08/739,703 and 08/843,409.

It is noted that although the Declaration claims benefit to provisional patent application 60/008,104, the priority information on page 1 does not reflect this claim.

7. The priority information on page 1 is confusing and not in proper form. It is suggested that the priority information on page 1 be amended to delete the information as presently constituted and to insert the following:

"This application for letters patent claims benefit of provisional patent application serial number 60/015,459, filed on April 15, 1996, now abandoned, having the same title of invention and the same inventors as the present application and claims benefit of provisional patent application number 60/008,104, filed on October 30, 1995, now abandoned. This application is a division of and claims priority to patent application serial number 08/843,409, filed April 15, 1997, now US Patent No. 6,103,235 which is a continuation-in-part of patent application number 08/739,703, filed October 29, 1996, now abandoned."

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CAR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CAR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CAR 3.73(b).

Claims 1-4, 6, 9-10 and 22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 3-8 of U.S. Patent No.6,103,235 in view of Thompson (JBC, 1995, 270:28037-28041, IDS item).

US Patent No. 6,103,235 is generic to the currently claimed invention. Although the conflicting claims are not identical, they are not patentably distinct from each other because they relate to the same inventive concept. The instant claims are a species of the claims of the patented application and have all of the characteristics of a method of inhibiting a rejection response in a primate recipient by inducing immune tolerance in the primate recipient to foreign mammalian donor cells, tissue or organ comprising the steps of exposing the recipient to an anti-CD3-DT immunotoxin with reduced anti-DT antibody binding so as to reduce the recipients T-cell lymphocyte population by at least 80% and transplanting the donor cells, tissue or organ into the recipient such that a rejection response by the recipient to the donor cell, tissue or organ is inhibited, the method further comprising administering an immunosuppressant compound wherein the compound is

deoxyspergualin, wherein the immunosuppressant compound blocks IL-12-induced induction of gamma interferon, wherein the immunosuppressant is administered beginning from about 0 to 6 hours before the transplanting step. It is noted that the instantly claimed sFv-DT390 has reduced anti-DT antibody binding.

Thompson et al teach sFv-DT390, a single chain anti-CD3-immunotoxin, which can bypass the inhibitory effect of pre-existing anti-DT antibodies (p. 28037, col 2). Advantages of the construct over other anti-CD3-immunotoxins for the treatment of transplant rejection include its low molecular weight, allowing it to penetrate tissue, pre-existing anti-DT antibodies in human sera are only partially blocked, it would have less HAMA effect than other known anti-CD3 immunotoxins, its production cost is low. Given the known advantages of sFv-DT390 over other anti-CD3 immunotoxins it would have been *prima facie* obvious to one of ordinary skill in the art and one would be motivated to substitute the known sFv-DT390 of Thompson et al for the generic anti-CD3-immunotoxin of the patented claims with a reasonable expectation of success.

If Applicant were able to overcome the rejection above, the claims would still be rejected because the claims of claims a method using a generic immunotoxin which effectively covers the newly claimed

Claims 1-4, 6, 9-10 and 22 would still be rejected under the judicially created doctrine of double patenting over claims 1 and 3-8 of US Patent No. 6,103,235 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows set forth above.

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent. *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

10. The specification is objected to and claims 1-4, 6, 9-10 and 22 are rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from a written description (e.g. sequenced); or (3) deposited.

The claims are drawn to sFv-DT390 which is derived from the antibody UCHT1 and a teaching is made of how to make the construct on page 50. However, it does not appear that all restrictions upon public access to the antibody

have been irrevocably removed or that viable samples of the antibody will be made available for the life of any patent issued. Since the variable domains for sFv-DT390 were isolated from mRNA isolated from UCHT1 hybridoma cells provided by Dr. P.C. Beverly, Imperial Cancer Research Fund in London (see page 65, lines 20-30) and the invention requires amplification of the coding sequences of the VL and VH regions of UCHT1 antibody, UCHT1 is a critical element to the practice of the invention. Further, no sequence information has been provided that would adequately describe the VL and VH domains.

It is unclear if a cell line which produces an anti-CD3 immunotoxin having the exact structural and chemical identity of sFv-DT390 is known and publicly available, or can be reproducibly isolated without undue experimentation. Clearly, without access to a hybridoma cell line producing immunotoxin sFv-DT390 it would not be possible to practice the claimed invention. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed immunotoxin; (2) a cell line which produces the chemically and functionally distinct immunotoxin claimed; and/or (3) the claimed immunotoxin's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies

with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed immunotoxin species, sFv-DT390. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

Applicant has not disclosed the deposit of hybridoma cell lines that would reproduce the immunotoxin sFv-DT390.

If a deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent

in U.S. patent applications. Applicant's provision of these assurances would obviate this objection/rejection.

Affidavits and declarations, such as those under 37 C.F.R. § 1.131 and 37 C.F.R. § 1.132, filed during prosecution of the parent application do not automatically become a part of this application. Where it is desired to rely on an earlier filed affidavit, the applicant should make the remarks of record in the later application and include a copy of the original affidavit filed in the parent application

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of the deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

11. Claims 1-4, 6, 9-10 and 22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The claims are drawn to a method of inhibiting a rejection response in a primate recipient by inducing immune tolerance. It is noted that Auchincloss

(chapter 11 in Transplantation Immunology, Bach and Auchincloss Eds. Wiley-Liss, New York, 1995, pages 211-218) specifically teaches that tolerance is the long-lasting nonreactivity of the immune system to a specific set of antigens, maintained without on-going immunosuppression, see page 211. The specification teaches that transplant tolerance remains an elusive goal and physicians would like to see successful, allogeneic organ transplant without the necessity for indefinite non-specific maintenance with immunosuppressive drugs (p. 2) and teaches that the present invention meets the need by providing a method of inducing immune tolerance (p. 3). The specification teaches a method of inducing immune tolerance by administering an immunotoxin to reduce recipient's peripheral blood T-cell lymphocyte population by at least 80% (p. 17) and teaches that the method can further include administering corticosteroids, donor leukocytes, immunosuppressants (p. 18). The specification exemplifies the survival of allografted monkeys with CD3 immunotoxin alone wherein they survived 51-79 days (page 97), 51, >165 days (page 84) with extended survival for those animals that had additional immunosuppressive treatment (page 84) and specifically teaches that following depletion, complete T-cell recovery occurs in three to four weeks (page 82). One cannot extrapolate the teaching of the specification to the scope of the claims because it is clear that although immunosuppression is achieved with the claimed method, immune tolerance, as taught by the specification has not been achieved. The specification, in agreement with Auchincloss, clearly teaches that "immune tolerance" is meant to be tolerance that allows transplant recipients to go without the necessity for indefinite non-specific maintenance with

immunosuppressive drugs (see page 2). It is clear that the instant method does not provide immune tolerance. Further, the unpredictability of the art is exemplified by both Auchincloss, *Supra,* Monaco (Immunomethods, 1993, 2:159-170) and Wee et al (Transplantation, 1994, 58:261-264). Auchincloss teaches, at the Conclusion on page 217, that although more than a dozen different techniques to induce tolerance in rodents are now available, the fact remains that none of them has been used successfully in the clinic. Inducing transplantation tolerance in humans must therefore be very hard to do, thus those reading this chapter should be wary of simple solutions to this complex process. Monaco discloses that the induction of specific tolerance to tissue allografts and xenografts continues to be a subject of intense experimentation, however significant problems remain (see Abstract). In reviewing the experimental evidence, Monaco points out the species and model dependency of achieving transplantation tolerance (see entire document). Further, Wee et al. disclose the art-known experience that permanent allograft acceptance has not been achieved in any of the large animal models (first paragraph) and the permanent allograft acceptance is much more difficult to induce in higher animals that in previously reported rodent models (last paragraph) (Transplantation, 1994). Based on the information in the art and the statements in the specification drawn to the elusiveness of the goal of transplant tolerance, it could not be predicted that the invention would function as claimed. In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective tolerance-induction therapies, undue experimentation would be required to practice the claimed therapeutic *in vivo* methods with a reasonable expectation of success,

absent a specific and detailed description in applicant's specification of how to effectively practice the claimed *in vivo* methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inducing immune tolerance.

Applicant is invited to consider alternative therapeutic endpoints such as immunosuppression in contrast to the claimed therapeutic endpoint of tolerance.

12. Claims 1-4, 6, 9-10 and 22 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1-4, 6, 9-10 and 22 are indefinite because claim 1 recites "sFv-DT390" as the sole means of identifying the immunotoxin. The use of laboratory designations only to identify a particular immunotoxin renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct immunotoxins. Amendment of the claims to include the depository accession number of the immunotoxin is required, because deposit accession numbers are unique identifiers which unambiguously define a given immunotoxin.

Claims 1-4, 6, 9-10 and 22 are indefinite because claim 1 recites "reducing T-cell lymphocyte population by at least 80%". The claims are confusing because it is not clear what the reduction is compared to. For example, is the reduction compared to normal control?

Claims 1-4, 6, 9-10 and 22 are indefinite because claim 1 recites "exposing the recipient". The claims are confusing because it is not clear what is meant by the

term "exposing", for example, is the immunotoxin shown to the recipient, is it applied topically? The rejection can be obviated by amending the claim to delete the term "exposing" and substituting, for example "administering"

Claim 22 is indefinite in the recitation of the phrase "said immunosuppressant". There is no antecedent basis for the limitation in claim 1 from which claim 22 depends.

Claim Rejections - 35 USC § 103

13. Claims 1-4 are rejected under 35 USC 103 as being unpatentable over Thompson et al (JBC 1995, 270:28037-28041, IDS item) in view of US Patent No. 5,725,857.

The claims are drawn to a method of inhibiting a rejection response in a primate recipient by inducing immune tolerance in the primate recipient to foreign mammalian donor cells, tissue or organ comprising the steps of exposing the recipient to sFv-DT390 with reduced anti-DT antibody binding so as to reduce the recipients T-cell lymphocyte population by at least 80% and transplanting the donor cells, tissue or organ into the recipient such that a rejection response by the recipient to the donor cell, tissue or organ is inhibited.

Thompson et al teach that FN18-CRM9, a rhesus monkey analog of UCHT1-CRM9, is capable of depleting circulating T cells and resident T cells in the lymph nodes, of delaying skin allograft rejection as compared to antibody treatment and of being used as an adjuvant in inducing tolerance to mismatched kidney transplants (Page 28037, col 1). Thompson et al teach that there is a problem using FN18-CRM9, UCHT1-CRM9 and other diphtheria toxin (DT)-based immunotoxins in the

treatment of disease in animals that have anti-DT antibodies. This problem has been encountered both in humans and in rhesus monkeys (p. 28037, col 2). Thompson et al teach that sFV-DT390, derived from UCHT1, can bypass the inhibitory effect of the pre-existing anti-DT antibodies (page 28037, col 1) and teach that the advantages of the construct over other anti-CD3-immunotoxins include its low molecular weight which allows it to penetrate tissue and low production costs. Thompson et al do not teach substituting sFv-DT390 for FN18-CRM9.

US Patent No. 5,725,857 specifically teaches that antibody FN18 is the monkey equivalent of the human anti-CD3 (UCHT1) and is known to bind to the same CD3 receptor epitopes as bound by the human CD3 antibody and is the same isotype as the human CD3 antibody. Thus in terms of the parameters relevant for predicting successful T cell depletion, UCHT1-CRM9 and FN18-CRM9 are expected to have the same activity (see attached USPATFUL printout showing the key words in context..

It would have been *prima facia* obvious for one of ordinary skill in the art at the time the invention was made, and one would have been motivated, to have substituted UCHT1-CRM9 for the FN18-CRM9 of the methods of Thompson et al, in the methods by Thompson et al, because as taught by US Patent No. 5,167,956, the immunotoxins are functional equivalents in that they are known to bind to the same epitopes and to be of the same isotype and thus in terms of successful T cell depletion, the two immunotoxins are expected to have the same activity. Further, it would have been *prima facie* obvious at the time the invention was made, and one would have been motivated to substitute sFv-DT390 for the substituted functional

equivalent because Thompson et al specifically teach the advantages of the construct over the other anti-CD3 immunotoxins since it can bypass the inhibitory effect of pre-existing anti-DT antibodies and because of its low production costs and because its low molecular weight allows it to penetrate tissues. Although the references do not specifically teach T-cell deletion by 80%, the claimed method appears to be the same as the prior art method of the combined references, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the method of the combined prior art does not possess the same material, structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from the method of the combined prior art preferences and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

14. Claims 1-4, 6, 9-10 and 22 are rejected under 35 USC 103 as being unpatentable over Thompson et al (JBC 1995, 270:28037-28041) in view of US Patent No. 5,725,857 as applied to claims 1-4 and further in view of Lu et al (J. Am. Soc. Nephrol., 1993, 4:1239-1256).

The claims are drawn to a method of inhibiting a rejection response in a primate recipient by inducing immune tolerance in the primate recipient to foreign mammalian donor cells, tissue or organ comprising the steps of exposing the recipient to sFv-DT390 with reduced anti-DT antibody binding so as to reduce the recipients T-cell lymphocyte population by at least 80% and transplanting the donor

cells, tissue or organ into the recipient such that a rejection response by the recipient to the donor cell, tissue or organ is inhibited, the method further comprising administering an immunosuppressant compound wherein the compound is deoxyspergualin, wherein the immunosuppressant compound blocks IL-12-induced induction of gamma interferon, wherein the immunosuppressant is administered beginning from about 0 to 6 hours before the transplanting step.

The combined prior art references teach as set forth above but do not teach a method further comprising administering an immunosuppressant compound, wherein the compound is deoxyspergualin, wherein the immunosuppressant compound blocks IL-12-induced induction of gamma interferon, wherein the immunosuppressant is administered beginning from about 0 to 6 hours before the transplanting step.

Lu et al teach that deoxyspergualin effectively prevents and treats rejection in animals and in human trials (p. 1246 see Other Drugs) and further teaches that steroids (which include corticosteroids) are important immunosuppressive drugs which have significant inhibitory actions at a number of different stages of allograft rejection (see p. 1242, col 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, and one would have been motivated, to combine the previously combined references and Lu et al because Lu et al specifically teach that deoxyspergualin is an important drug in the treatment and prevention of rejection and animals. The timing for the administration of the immunosuppressant is obvious because the claimed protocol was standard and well known in the art.

Although the references do not specifically teach deoxyspergualin blocks IL-12-induced induction of interferon gamma, the claimed method appears to be the same as the prior art method of the combined references, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the method of the combined prior art does not possess the same material, structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from the method of the combined prior art preferences and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

15. No claims allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
March 21, 2001

Application No. 09/353,695

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

☑ 1. This application clearly fails to comply with the requirements of 37 CFR 1.821 - 1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☑ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).

☐ 7.

Other: _____

Applicant must provide:

☑ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing"

☐ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification

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